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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/506,893	09/01/2005	Sabine Eming	3030-101	6739

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EXAMINER	
SAOUD, CHRISTINE J	
ART UNIT	PAPER NUMBER
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/506,893	EMING ET AL.	
	Examiner	Art Unit	
	Christine J. Saoud	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 February 2007 and 10 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-7,9-15 and 17-20* is/are pending in the application.

4a) Of the above claim(s) *17-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-7 and 9-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/1/05, 12/1/05, 12/8/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

Claims 2, 8, and 16 have been canceled. Claims 1, 3, and 12 have been amended. Claims 1, 3-7, 9-15 and 17-20 are currently pending.

Election/Restrictions

Applicant's election without traverse of Group I in the reply filed on 12 February 2007 is acknowledged.

Claims 17-20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 12 February 2007.

Sequence Compliance

The statement that was submitted with the Sequence Listing is not sufficient and does not meet the requirements of 37 CFR 1.821(f), which requires a statement that the content of the paper and computer readable copies are the same. Applicant's statement that "the sequence listing submitted wherewith does not extend beyond the original disclosure" is not sufficient.

The instant specification fails to comply with the Sequence rules (37 CFR 1.821(d)) at pages 4, 6 and 7. In addition to reference to sequences with no sequence identifiers, the specification, including the claims, fails to use the proper format for referencing a sequence identifier (SEQ ID NO:). Applicant should be sure to include a

sequence identifier for each amino acid or nucleic acid sequence provided in the specification as well as use the appropriate format for making such a reference.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

The information disclosure statement (IDS) submitted on 9/1/05, 12/1/05, 12/8/06 have been considered by the examiner. The IDS submitted on 9/1/05 was a duplicate of the IDS submitted on 12/8/06, therefore, one of the IDS's was crossed through and the other was initialed and signed.

The Scharffetter-Kochanek et al. reference has been considered only in so far as the Examiner reads and understands German.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-7, and 9-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for alteration of a plasmin cleavage site

by substitution of amino acids corresponding to positions 110 and/or 111 of VEGF165 in a VEGF molecule, does not reasonably provide enablement for alteration of positions corresponding to positions 109 or 112. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claimed invention is directed to VEGF molecules in which the plasmin cleavage site at amino acid positions 110/111 (corresponding to those positions in VEGF165) has been altered to prevent proteolytic degradation. The claims encompass mutation/deletion of amino acids 109 to 112 in this region of the molecule. However, amino acids 109 and 112 are not involved in this process, so there is no reasonable expectation that modification of these positions will have any biological effect on the molecule such that the VEGF molecule is not susceptible to plasmin degradation. It is not clear how the molecule should be altered at these amino acid positions to obtain a VEGF molecule that is useful. Therefore, it would require undue experimentation to make and use the invention commensurate in scope with the claims, absent evidence to the contrary.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3-7, 9-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims refer to "a vascular endothelial growth factor variant" having an amino acid sequence, wherein amino acid positions are deleted or replaced. However, there is no antecedent basis for the recited positions because there is no reference to any particular amino acid sequence. The art recognizes a number of different VEGF molecules, therefore, the recitation that the claims are directed to a VEGF variant are indefinite because the metes and bounds of what is encompassed by the claims are unclear. Based on the disclosure of the specification, it would appear that VEGF121, VEGF145, VEGF165, VEGF183, VEGF189 and VEGF206 are the VEGF molecules to be encompassed by the claims in that these molecules actually possess the amino acid positions recited in the claims.

Claim 1 is unclear and indefinite for the contradictory limitation of "at least one amino acid at positions 109 to 112 of the native vascular endothelial growth factor is replaced by another amino acid or is deleted, wherein said at least one amino acid in the sequence of the native vascular endothelial growth factor at positions 109 to 112 is replaced by proline". If a single amino acid is deleted, it is not clear how that amino acid can now be replaced by proline. The recitation of "at least one" encompasses one change, which can be a replacement or deletion – if it is a deletion, then the "wherein" clause makes no sense.

Claim 1 lacks antecedent basis for "said sequence is the amino acid sequence of the native vascular endothelial growth factor".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 3-7, 9-11 and 13-15 are rejected under 35 U.S.C. 102(a) as being anticipated by Lauer et al. (FEBS Letters 531: 309-313, 2002).

Lauer et al. teach the substitution of Arg110 with Ala or Gln and the substitution of Ala11 with Pro in VEGF165 to produce a plasmin-resistant and biologically active VEGF165 mutein, thereby anticipating the claims. Lauer et al. used site-directed mutagenesis (see Materials and Methods).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3-7, and 9-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lauer et al. (FEBS Letters 531: 309-313, 2002) in view of U.S. Pat. No. 5,219,739.

The disclosure of Lauer et al. is as described above. Lauer et al. do not teach the use of a signal sequence for the production of a VEGF variant. However, U.S. Pat. No. 5,219,739 teaches the native nucleic acid and amino acid sequence for VEGF121, which includes the native signal sequence. Signal sequences are used by eukaryotic host cells to secrete recombinant protein or direct it to the proper organelle in the cell. It would have been prima facie obvious to one of ordinary skill in the art to use the native signal sequence for the production of the VEGF molecules of Lauer et al. because such signal sequences are found in nature and can be used by host cells to secrete recombinant protein or direct the protein to the proper organelle in the cell during protein expression. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time it was made, absent evidence to the contrary.

Claims 1, 3-7, and 9-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Keyt et al. (J. Biol. Chem. 271(13): 7788-7795, 1996) and Lauer et al. (J. Invest. Dermatol. 115: 12-18, 2000) in view of Market et al. (Protein Engineer. 14(10): 791-796, 2001) and U.S. Pat. No. 5,219,739 (Tischer et al.).

Keyt et al. teach that VEGF contains a plasmin cleavage site at amino acid positions Arg110 and Ala111. Keyt et al. also teach that loss of one or more carbohydrate domains, such as with plasmin cleavage, results in significantly reduced endothelial cell proliferation by VEGF administration (see page 7794, column 2, first full paragraph). Therefore, plasmin cleavage and proteolytic processing of VEGF results in significantly reduced biological activity. Lauer et al. teach that chronic wounds produce more plasmin. Lauer et al. also teach that VEGF is very important for healing of wounds, that plasmin degrades VEGF165 and that administration of protease inhibitors stabilize VEGF (see page 15). Neither reference teaches a VEGF variant wherein amino acid positions 110 and/or 111 have been mutated or deleted.

Market et al. teach site-directed mutagenesis to provide proteolytic resistance to enzymatic degradation. Tisher et al. teach the amino acid and nucleic acid sequences for VEGF121 and VEGF165, including the native signal sequence for the molecules.

It would have been prima facie obvious to one of ordinary skill in the art at the time the instant invention was made to make a VEGF molecule that was resistant to plasmin cleavage using the methods of Market et al. and the starting materials of Tisher et al., including mutation of the amino acids in the cleavage site, identified by Keyt et al. One would be motivated to make such a mutant because Keyt et al. teach that VEGF is susceptible to degradation by plasmin, and this degradation results in a VEGF molecule which is less biologically active. Furthermore, Lauer et al. suggest that in chronic wounds, there is more plasmin which degrades the VEGF and this degradation may play a role in the chronic wound environment. One would have a reasonable

expectation of success in making such mutants because Market et al. used a similar technique to provide resistance in another biological molecule which was susceptible to plasmin cleavage. Therefore, the invention as a whole would have been prima facie obvious at the time it was made, absent evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine J. Saoud whose telephone number is 571-272-0891. The examiner can normally be reached on Monday-Friday, 6AM-2PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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PRIMARY EXAMINER
Christine J. Saoud